IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Jean-Francois Bouquet et al.
U.S. Appln. No.	:	10/657,126
U.S. Filing Date	:	September 9, 2003
Title of Invention	:	IMMORTAL AVIAN CELLS
Confirm No.	:	9209
Examiner	:	Robert A. Zeman
Art Unit	:	1645

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FILED VIA *EFS-WEB*

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
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Dear Sir:

I, Michel Riviere, declare and state that:

1. I make this declaration in connection with U.S. application Serial No. 10/657,126. I am familiar with its prosecution history, particularly the Office Action mailed on June 1, 2007, as it pertains to the rejection under 35 U.S.C. §103(a) of claims 11-13 and 15-19 as allegedly being unpatentable over Evan (1993) and Givol *et al.* (1994; hereinafter "Givol").

2. I am a citizen of France. As indicated on my attached *Curriculum vitae*, I obtained a doctorate degree in Veterinary Medicine from the National Veterinary School of Lyon. I have been involved in a number of research areas, particularly recombinant vaccines. I have served as the Director of Intellectual Property at Merial LTD., the assignee of this application, since 1998. In view of my education and experience, I consider myself to be an expert in the field to which this application pertains.

3. The claimed invention relates to untransformed, immortalized avian cells that contain and express nucleic acid molecules encoding an anti-apoptotic protein. As the Examiner points out,

Evan relates to cells and cell lines comprising a bcl-2 gene wherein said gene is inserted into a vector that is integrated into host cells. Evan states that the host cells can be (i) from a multicellular organism, (ii) immortalized cells, and (iii) from tumours. The Examiner relies on Givol's disclosure of chicken embryo fibroblasts which contain a retroviral vector encoding the bcl-2 gene. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to utilize chicken embryo fibroblasts as host cells for the vector disclosed by Evan. The Examiner also asserts that there would have been a reasonable expectation of success as Evan discloses a method wherein any cells from a multicellular organism can be used, and Givol has demonstrated that chicken embryo fibroblasts can be used to express a vector-based bcl-2 gene.

4. Contrary to the Examiner's assertion, one of ordinary skill in the art would not have arrived at the present invention by combining Evan and Givol. Firstly, there is no evidence that the method described in Evan can be used with any multicellular organism that includes avian, or with immortalized and untransformed cells from any multicellular organism. Evans teaches on page 17 lines 22-26 that "Although the survival-promoting functions of *bcl-2* are well described in lymphoid cells... there has been no suggestion that this may be a generally applicable situation with respect to multiple tissue types". Evan only demonstrates the method in Rat-1 fibroblasts expressing the cMyc polypeptide (Example 3), hybridomas (Example 5), and in cells derived from embryonic central nervous system, lymphoid cells, and haematopoietic cells (Example 6). None of these cells are immortalized, untransformed, and avian. Givol also does not provide any teaching of immortalized, untransformed, avian cells comprising the bcl-2 gene. Givol specifically indicates that the cells are not immortalized (paragraph bridging pages 23 and 24) "Since the CEF [chicken embryo fibroblast] are not immortalized, nor are these cells immortalized in the course of the experiments either by c-Myc or by Bcl-2, the normal processes that control growth and division are not perturbated". Further, while Givol states that "the morphology of the cells, their inability to grow in soft agar, the longevity of the cells cultured in the presence of normal levels of serum (23-25 passages) were essentially the same for cultures infected either with RCASBPbcl-2 or with RCASBP vector"; 23 to 25 passages correspond to the period preceding the cell crisis. It is known in the art that, in order to establish the immortalized and untransformed characteristics, cells need to be cultured for over 100 passages. Hence, Givol does not teach cells that are immortalized, and one skilled in the art would not recognize that Givol alone or in combination with Evan teaches cells that are immortalized and

untransformed. With this in mind, the skilled artisan could not arrive at the present invention by simply using the cells of Givol in the method of Evan.

5. Notably, there would be no motivation to try the present invention, as the state of the art at the time that the present application was filed teaches against trying to immortalize avian cells and against trying to produce immortalized, untransformed cells using the SV40 large T antigen. Immortalization of avian cells is difficult to achieve, and there was very little evidence in the scientific literature which discloses successful immortalization of avian cells. In fact, some sources noted the difficulty associated with immortalizing avian cells. For example, Darnell et al. (Molecular Cell Biology, 1960; attached herein) indicates that "[t]he ease with which transforming stimuli can generate immortal cell lines from cell strains depends on underlying propensity of the cells to spontaneously acquire immortality...Adherent chicken cells are almost never immortalized" (page 967). Similarly, Guilhot et al. (Oncogene 8: 619-624, 1993; attached herein) indicates that "[i]mmortalization by oncogenes from DNA tumor virus has been widely described in the mammalian species...but never in avian species, in which immortalization efficiency is very low" (page 619). Hence, it was known in the art at the time of filing that immortalization of avian cells is an unlikely event.

6. In addition, it was also known in the art that the SV40 large T antigen induces transformation in cells. As indicated in Guilhot et al., the two most extensively studied anti-oncogene proteins are the RB and p53 products. While the adenoviral E1A or E1B products or the E6 or E7 protein of human papillomavirus inactivates either the RB or p53 product, SV40 large T antigen inactivates both anti-oncogene products. Hence, it is very likely that the SV40 large T antigen will induce tumorigenic characteristics in cells. This is supported in the art. For example, WO 92/10563 indicates that rabbit epithelial and endothelial cells transfected with a vector expressing SV40 T+t antigen present a tumorigenic phenotype, i.e., has the ability to grow and to form colonies in soft agar culture. Sompayrac et al. (Mol Cell Biol 4: 1661-1663, 1984) indicates that F111 rat cells transfected by a plasmid coding for SV40 T+t antigen are also tumorigenic (see table 2). Thus, one skilled in the art would expect that expression of SV40 T+t antigen is tumorigenic.

7. Therefore, to arrive at the immortalized, untransformed cells of the present invention, one skilled in the art (1) would not try to immortalize avian cells given the difficulty in achieving immortalized avian cells; and (2) would not try to immortalize cells using SV40

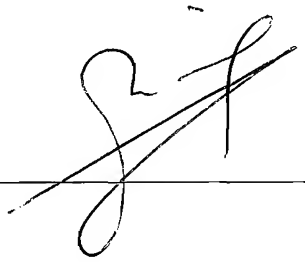
large T antigen, considering the likelihood that the cells would exhibit tumorigenic characteristics. Consequently, the skilled artisan would not try the present invention.

8. It is also important to note that the present invention fits a specific need in the art. Immortalized, untransformed avian cells are useful for multiplying vaccine viruses. However, these cells do not have the ability of growing on top of each other and therefore undergo cell death by apoptosis upon reaching confluence. In order to defer the apoptotic process at confluence, the immortalized, untransformed cells of the invention express an anti-apoptotic protein, which allows the cells to sustain and survive in culture at a confluence state while increasing the cellular density for the production of vaccinal viruses. Thus, the present invention fulfills a specific need that is not taught or even suggested in the cited references.

9. The arguments presented herein demonstrate that the skilled artisan would not have been motivated by the cited references or the state of the art to arrive at the claimed invention. Therefore, I believe that the claimed invention is not obvious over the cited references.

10. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. These statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 03-07-2008



Michel Riviere